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PERIPHERAL

Paclitaxel-Coated Balloon in Infrapopliteal Arteries

12-Month Results From the BIOLUX P-II Randomized Trial (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries)

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ABSTRACT

OBJECTIVES The aim of BIOLUX P-II (BIOTRONIK'S–First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries) trial was to compare the safety and efficacy of a novel paclitaxel-coated drug-eluting balloon (DEB) versus an uncoated balloon (percutaneous transluminal angioplasty [PTA]) in de novo or native restenotic lesions of the infrapopliteal arteries in patients with claudication and critical limb ischemia.

BACKGROUND DEB have shown promising results in femoropopliteal lesions, but data for infrapopliteal lesions are scarce.

METHODS In this prospective, multicenter, randomized first-in-man study, 72 patients were randomized 1:1 to either a Passeo-18 Lux DEB (Biotronik AG, Buelach, Switzerland) (n = 36) or Passeo-18 PTA (n = 36). Follow-up assessments were scheduled at 1, 6, and 12 months, with angiographic assessment at 6 months. Adverse events were adjudicated by an independent clinical events committee, and angiographic parameters were assessed by an independent core laboratory.

RESULTS The primary safety endpoint (a composite of all-cause mortality, target extremity major amputation, target lesion thrombosis, and target vessel revascularization at 30 days) was 0% in the DEB group versus 8.3% in the PTA group (p = 0.239). The primary performance endpoint (patency loss at 6 months) was 17.1% in the DEB group versus 26.1% in the PTA group (p = 0.298), and major amputations of the target extremity occurred in 3.3% versus 5.6% of the patients at 12 months, respectively.

CONCLUSIONS The Passeo-18 Lux DEB has been proven to be safe and effective in infrapopliteal lesions with comparable outcomes to PTA. (J Am Coll Cardiol Intv 2015;8:1614–22) © 2015 by the American College of Cardiology Foundation.

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Peripheral artery disease of the lower extremities is the third leading cause of atherosclerotic cardiovascular morbidity and is increasing dramatically as the population ages (1,2). Infrapopliteal atherosclerosis is the most common cause of critical limb ischemia (CLI), which is associated with poor prognosis regarding limb preservation and survival in patients with tissue involvement (3). Patients with CLI have an increased risk for complications after open surgical revascularization, and therefore, an endovascular-first strategy is recommended in infrapopliteal lesions with stent placement being reserved as bail out option (3,4). Drug-eluting balloons (DEBs) appear to be a good alternative to percutaneous transluminal angioplasty (PTA) with uncoated balloons as they combine the advantage of drug delivery without the disadvantages of a permanent stent. Hence, they are thought to reduce restenosis rates, one of the major limitations of PTA. DEBs have been proven to be superior to PTA in several randomized trials in femoropopliteal lesions (5–8), but data in infrapopliteal lesions are scarce.

SEE PAGE 1623

The Passeo-18 Lux DEB (Biotronik AG, Buelach, Switzerland) is coated with paclitaxel, which is incorporated in a delivery matrix of n-Butyryl tri-n-hexyl citrate (BTHC). Promising results have been obtained using the same formulation in animal studies and coronary lesions (9,10) and using the Passeo-18 Lux in femoropopliteal lesions (8). The purpose of the BIOLUX P-II (BIOTRONIK'S-First in Man study of the Passeo-18 LUX drug releasing PTA Balloon Catheter vs. the uncoated Passeo-18 PTA balloon catheter in subjects requiring revascularization of infrapopliteal arteries) first-in-man trial was to prospectively evaluate the safety and performance of this novel DEB versus PTA for the treatment of stenotic, restenotic, or occluded infrapopliteal arteries excluding in-stent restenosis in patients experiencing claudication or CLI.

METHODS

STUDY DESIGN AND POPULATION. BIOLUX P-II is a prospective, international, multicenter, randomized, controlled, first-in-man study, aiming to assess the safety and performance of the Passeo-18 Lux paclitaxel-coated DEB versus the uncoated Passeo-18 balloon catheter (PTA) in patients with stenosis, restenosis, or occlusion of the infrapopliteal arteries (excluding in-stent restenosis and experiencing claudication or CLI).

The study is registered at ClinicalTrials.gov (NCT01867736), where the full set of inclusion and exclusion criteria is available. The main inclusion criteria were single or sequential de novo or restenotic lesions excluding in-stent restenosis (≥70% diameter reduction or occlusion) in the infrapopliteal arteries ≥30 mm, a maximum of 2 different vessels to be treated, reference vessel diameter of 2 to 4 mm based on visual estimation, in-flow free from flow-limiting lesion, at least 1 nonoccluded crural vessel with angiographically documented run-off to the foot, and successful wire crossing of the lesion. Main exclusion criteria were lesions extending beyond the ankle joint, acute thrombus in the target vessel, planned major amputation of the target limb, previous bypass surgery of the target vessel, or previous stent implantation in the target lesion. Randomization was performed after successful wire passage through the lesion via the electronic case report form. Patients were allocated to DEB and PTA in a 1:1 ratio, with block sizes of 4 and 6.

Prior to DEB treatment, lesion preparation was recommended to be performed with an uncoated balloon that was shorter and smaller than the DEB. Thereby, pre-dilation should follow current hospital practice. Pre-dilation for PTA lesions was not required. In case of insufficient treatment results, post-dilation with a Passeo-18 uncoated balloon was

ABBREVIATIONS AND ACRONYMS

ABI = ankle brachial index

BTHC = n-Butyryl tri-n-hexyl citrate

CLI = critical limb ischemia

DEB = drug-eluting balloon

MAE = major adverse event(s)

OPG = objective performance goal

PTA = percutaneous transluminal angioplasty

QVA = quantitative vascular angiography

TLR = target lesion revascularization

received consulting fees from Medtronic, Gore, Cook, Bard Peripheral Vascular, Covidien, Biotronik, and Abbott Vascular; serves on the advisory board of Medtronic, Boston Scientific, and Gore; and is a member of the advisory board or a consultant for Angioslide, Veryan, Cordis Corp., Spectranetics, Straub Medical, TriReme, and VIVA Physicians. Dr. Beschorner has received personal fees from Biotronik outside of the submitted work. Prof. Dr. Scheinert acts as a member/consultant of the advisory board of Abbott, Angioslide, Atheromed, Biotronik, Boston Scientific, Cook Medical, Cordis, Covidien, CR Bard, Gardia Medical, Hemoteq, Intact Vascular Inc., Medtronic, Ostial Inc., TriReme Medical, Trivascular, and Upstream Peripheral Technologies. Prof. Dr. Schulte is a member of the advisory boards of Bayer, Eurocor, Merck Sharp & Dohme, and Terumo; has received consulting fees/honoraria from Bard, Biotronik, Boston Scientific, Covidien, and Eurocor; and has received grant/research support from AstraZeneca, Bard, Biotronik, Boston Scientific, Eurocor, Covidien, IDEV, Lutonix, and Medac. Dr. Rastan has received consulting fees/honoraria from Terumo, Medtronic, Covidien, Abbott, Volcano, and Bard. Prof. Dr. Brodmann has received consulting fees from Medtronic, Bard, Covidien, and Biotronik. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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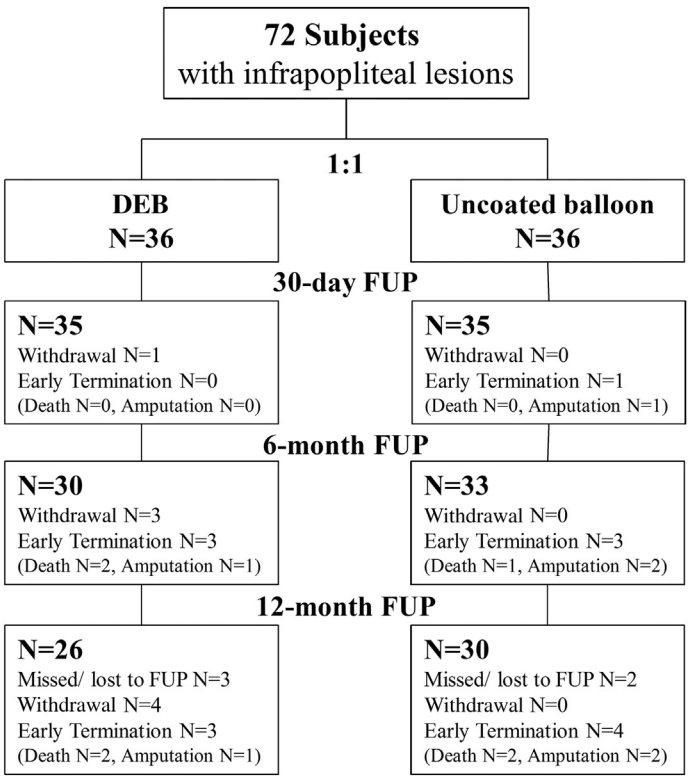
allowed, and in case of flow-limiting dissection, a bare-metal stent could be placed. Control arm angioplasty, as well as provisional stenting, should follow the manufacturer's current instructions for use. Dual antiplatelet therapy was recommended for 1 month post-procedure (acetylsalicylic acid 100 to 325 mg/day and clopidogrel 75 mg/day) and for 3 months in case of bailout stenting with a bare-metal stent. Clinical follow-up was scheduled at 30 days, 6 months, and 12 months, and angiographic follow-up at 6 months.

The study was conducted according to the Declaration of Helsinki, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice, and International Organization for Standardization's ISO 14155:2011, and approved by the respective independent ethical committees. All patients provided written informed consent prior to any study procedure. Monitoring included 100% source document verification. Quantitative vascular angiography (QVA) analysis was performed by an independent core laboratory (CoreLab Bad Krozingen GmbH, Bad Krozingen, Germany) that was blinded to the treatment, and all adverse events were adjudicated by an independent clinical events committee.

FIGURE 1 Patient Flow Diagram



Follow-up compliance was 91.7% for the DEB versus 100.0% for the uncoated balloon group at 6-month follow-up and 80.6% versus 94.4%, respectively, at 12-month follow-up. DEB = drug-eluting balloon; FUP = follow-up; PTA = percutaneous transluminal angioplasty.

STUDY DEVICES. The Passeo-18 Lux paclitaxel-coated balloon is identical to the Passeo-18 balloon catheter (Biotronik AG), but additionally is homogeneously coated with 3 μg paclitaxel per mm^2 balloon surface as a lipophilic antiproliferative substance. Paclitaxel is incorporated in a delivery matrix of BTHC as excipient, which incorporates paclitaxel into a microcrystalline structure to improve drug uptake into the vessel wall (9) and which degrades to citric acid and alcohol. Passeo-18 Lux is manufactured using a proprietary pipetting process designed to ensure homogenous coating distribution, 100% dosage control, and reproducible chemical and mechanical properties of the device. The unique combination of drug, excipient, balloon surface properties, and coating process is designed for the right balance between coating adhesion and drug release. Bare balloons are coated in an uninflated state, and homogeneity is controlled by making use of capillary effects. For the purpose of this study, the range of available sizes, which included sizes 3 to 7 mm, had been extended to include the small sizes 2.0 and 2.5 mm. Balloon lengths ranged from 40 to 120 mm.

ENDPOINTS AND DEFINITIONS. The primary safety endpoint was 30-day major adverse event (MAE) rate, defined as a composite of all-cause mortality, major amputation of the target extremity, target lesion thrombosis, and target vessel revascularization. The primary performance endpoint was 6-month target lesion primary patency, defined as <50% restenosis in the target lesion assessed by QVA without target lesion revascularization (TLR). Secondary endpoints were: 1) device success, defined as exact deployment according to instructions for use; 2) technical success, defined as successful vascular access, completion of procedure, and residual stenosis <30%; 3) procedural success, defined as device or technical success without the occurrence of MAEs during the hospital stay; 4) binary restenosis and 5) late lumen loss at 6 months assessed by QVA; 6) TLR; 7) target vessel revascularization and 8) MAE at 6 and 12 months; 9) change in ankle brachial index (ABI) and 10) Rutherford classification at 30 days, 6 months, and 12 months; and 11) quality of life at 6 and 12 months. Vessel calcification was assessed using the COMPLIANCE 360 score (11).

STATISTICAL ANALYSIS. On the basis of the assumption of a 65% binary restenosis rate in the PTA group and a 45% relative risk reduction in the DEB

group, it was calculated that a sample size of 46 lesions per group would yield a power of 80% considering a 2-sided test with a 5% significance level. Considering a 15% drop out rate and 1.5 lesions per subject, this corresponds to a final number of 36 patients/group. The endpoint analysis was performed on the basis of available data on the intention to treat population (i.e., subjects are analyzed in the groups to which they were randomized to and no subjects were excluded from analysis).

Continuous variables were summarized with mean ± SD. Categorical variables were summarized with frequencies and percentages. The following tests were applied when appropriate for group comparison: Student *t*, Mann-Whitney *U*, Fisher exact, chi-square, McNemar's, and log-rank tests. Survival analysis was carried out using the Kaplan-Meier estimator. The SAS statistical software (version 9.3, SAS Institute, Cary, North Carolina) was used for all statistical calculations.

RESULTS

BASELINE CHARACTERISTICS. Between July 2012 and June 2013, 72 patients were randomized in 6 centers in Europe to either Passeo-18 Lux DEB (n = 36, 50 lesions) or PTA (n = 36, 55 lesions) (Figure 1).

TABLE 1 Baseline Characteristics

	DEB (n = 36)	PTA (n = 36)	p Value
Male	27 (75.0)	30 (83.3)	0.384
Age, yrs	72.9 ± 10.3, 45–91	69.6 ± 8.9, 53–92	0.153
BMI, kg/m^2	27.9 ± 4.1, 22–39	27.4 ± 4.7, 18–43	0.736
Hypertension	31 (86.1)	31 (86.1)	>0.999
Hyperlipidemia	26 (72.2)	23 (63.9)	0.448
Smoking	20 (55.6)	20 (55.6)	>0.999
Current smoker	*4 (20.0)*	*6 (30.0)*	*0.716*
Diabetes	22 (61.1)	26 (72.2)	0.317
Insulin-dependent	*14 (63.6)*	*17 (65.4)*	*0.900*
History of previous PAD	17 (47.2)	22 (61.1)	0.237
Coronary artery disease	15 (41.7)	15 (41.7)	>0.999
Cerebrovascular disease	13 (36.1)	9 (25.0)	0.306
Renal insufficiency	10 (27.8)	10 (27.8)	>0.999
Cancer	3 (8.3)	3 (8.3)	>0.999
Rutherford class	4.5 ± 0.9, 2–5	4.4 ± 1.0, 2–5	0.915
2: moderate claudication	1 (2.8)	3 (8.3)	
3: severe claudication	7 (19.4)	5 (13.9)	0.915
4: ischemic rest pain	2 (5.6)	2 (5.6)	
5: minor tissue loss	26 (72.2)	26 (72.2)	

Values are n (%), mean ± SD, or minimum to maximum. Entries in *italics* represent subcohorts of the entire cohort of smokers and diabetic patients.

BMI = body mass index; DEB = drug-eluting balloon; PAD = peripheral artery disease; PTA = percutaneous transluminal angioplasty.

There was no significant difference in terms of baseline characteristics (Table 1). Mean age was 72.9 ± 10.3 years for DEB patients and 69.6 ± 8.9 years for PTA patients, and diabetes was present in 61.1% and 72.2%, respectively. Approximately three-fourths of patients had Rutherford class 5 (minor tissue loss), and one-half of the patients had a smoking history or a history of previous peripheral artery disease and concomitant coronary artery disease. Lesion and procedure details are depicted in Table 2. The DEB group had significantly less lesions without calcification than the PTA group (55.9% vs. 81.6%; p = 0.018), and more lesions with moderate to severe calcifications (26.5% vs. 7.9%; p = 0.056), all other parameters were not significantly different amongst the groups. Mean treated lesion lengths were 113.1 ± 88.1 mm and 115.0 ± 86.9 mm, respectively.

PROCEDURAL CHARACTERISTICS. Inflow lesions were treated in 50% of the patients in the DEB and 30.6% of the patients in the PTA group (p = 0.093). Overall, 139 balloons were used to treat 105 target lesions. Mean device diameter was 2.5 mm (range 2.0 to 4.0 mm) (Table 3). No bailout stenting was required. Minimum lumen diameter increased from 0.63 ± 0.63 mm and 0.62 ± 0.53 mm at baseline to 1.59 ± 0.46 mm and 1.59 ± 0.65 mm, respectively, post-procedure (Table 2).

ENDPOINTS. The primary safety endpoint, MAE at 30 days, occurred in none (0.0%) of the patients in the DEB group versus in 8.3% of the PTA group. At 12 months, 41.1% (DEB) versus 39.1% (PTA) of the patients experienced an MAE event, and 3.3% versus 5.6% experienced a major amputation of the target extremity (Table 4). All patients experiencing a major amputation were in Rutherford class 5 (minor tissue loss) at baseline, had diabetes, and presented with a reference vessel diameter of ≤2.5 mm. One target lesion thrombosis occurred in the PTA group.

The primary performance endpoint, lesion-based patency loss at 180 days by QVA, was observed in 17.1% of DEB lesions and 26.1% of PTA lesions; subject-based primary patency loss was 20.3% and 26.6%, respectively. At 6 months, the Kaplan-Meier curves for patency loss and TLR (clinically- and not clinically-driven) increased sharply (Figure 2); notably, 80% of the TLR in the DEB group occurred during 6-month angiography. At 12 months, patency loss occurred in 20 lesions (50.8%) in the DEB and 22 lesions (45.6%) in the PTA group. Overall, lesions requiring a TLR were totally occluded at baseline in 70% (DEB) and 50% (PTA) of the cases, with lesion length ranging between 80 to 302 mm (DEB) and 40 to 279 mm (PTA). Late lumen loss at 6 months was 0.56

TABLE 2 Lesion Characteristics at Baseline and Follow-Up Per Core Laboratory Assessment

	Baseline*		
	DEB	PTA	p Value
n	50	54	
Lesion location			
Anterior tibial artery	24 (48.0)	25 (46.3)	
Posterior tibial artery	11 (22.0)	12 (22.2)	0.693
Peroneal artery	7 (14.0)	11 (20.4)	
Tibioperoneal trunk	5 (10.0)	2 (3.7)	
Other	3 (6.0)	4 (7.4)	
Calcification†			–
None	19 (55.9)	31 (81.6)	0.018
Mild	6 (17.6)	4 (10.5)	0.501
Moderate	1 (2.9)	0 (0.0)	0.472
Moderate/severe	3 (8.8)	1 (2.6)	0.338
Severe	5 (4.7)	2 (5.3)	0.243
Moderate to severe	9 (26.5)	3 (7.9)	0.056
Thrombus present	0 (0.0)	0 (0.0)	>0.999
Treated lesion length, mm	113.1 ± 88.1, 24–351	115.0 ± 86.9, 39–295	0.960
MLD, mm	0.63 ± 0.63, 0.0–1.78	0.62 ± 0.53, 0.0–1.64	0.986
RVD, mm	2.28 ± 0.54, 1.40–4.02	2.19 ± 0.57, 1.21–3.93	0.246
Stenosis pre-procedure	72.5 ± 25.4, 31–100	72.1± 23.2, 30–100	0.936
Number of crural vessels with run-off the foot	1.7 ± 0.8, 0–3	1.7 ± 0.9, 0–3	0.565
Lesions per subject (n = 72)			
1	24 (66.7)	20 (55.6)	0.375
2	10 (27.8)	14 (38.9)	
3	2 (5.6)	2 (5.6)	
Post-Procedure			
n	48	52	
MLD, mm	1.59 ± 0.46, 0.81–2.88	1.59 ± 0.65, 0.0–3.94	0.888
Stenosis, %	29.7 ± 11.0, 13.5–55.0	30.5 ± 16.5, 2.0–100.0	0.796
6 Months			
n	32	30	
Binary restenosis			
At 6-month interval	17 (53.1)	12 (41.4)	0.359
At 180 days‡	6 (14.6)	10 (20.1)	0.480
MLD, mm	1.04 ± 0.81, 0.0–2.43	1.02 ± 0.76, 0.0–2.48	0.921
Stenosis, %	56.9 ± 30.7, 13.8–100.0	51.1 ± 31.3, 10.7–100.0	0.454
Late lumen loss, mm	0.56 ± 0.65 (0.3-0.8), −0.48–1.79	0.54 ± 0.66 (0.3-0.8), −0.43–1.93	0.913

Values are n (%); mean ± SD, minimum to maximum; or mean ± SD (95% confidence interval), minimum to maximum. *1 lesion of the uncoated balloon group without data. †16 lesions in each group without information; mild: calcium deposits <180° (on 1 side of vessel) in circumference and <50% of total lesion length; moderate: calcium <180° in circumference and ≥50% of length; moderate/severe: calcium ≥180° in circumference and <50% of length; severe: calcium ≥180° in circumference and ≥50% of lesion length (11). ‡Per Kaplan-Meier estimate.

MLD = minimal lumen diameter; NA = not available; RVD = reference vessel diameter; other abbreviations as in Table 1.

± 0.65 mm for DEB lesions versus 0.54 ± 0.66 mm for PTA lesions (p = 0.913) (Table 4). Notably, the core laboratory assessed 2 PTA lesions as 1, so that the number of lesions per core laboratory is 54.

Comparing CLI with non-CLI patients, MAE estimates at 12 months were 46.9% (n = 11) versus 25.0% (n = 2) for the DEB group (p = 0.362) and 39.7% (n = 11) versus 37.5% (n = 3) for the PTA group (p = 0.913). Lesion-based TLR estimates were 34.6% (n = 11) versus 12.5% (n = 1) (p = 0.257) and 31.6% (n = 11) versus 28.6% (n = 4) (p = 0.881), respectively.

Excluding patients with major amputation, mean Rutherford class improved from 4.5 ± 0.9 at baseline to 2.3 ± 2.3 at 6 months in the DEB group and from 4.4 ± 1.0 to 2.7 ± 2.4 in the PTA group (Figure 3). Including patients with major amputation and counting them as Rutherford class 6, Rutherford class at 6 months was 2.4 ± 2.3 in the DEB group and 2.9 ± 2.4 in the PTA group. No patient in the DEB group had a worsening of Rutherford class versus 6.3% in the PTA group.

Clinical outcomes at 30 days; Rutherford classification at 1, 6, and 12 months; quality of life (EQ-5D [EuroQol 5 Dimensions]) questionnaire; and ABI measurements are provided in the Online Appendix (Online Tables S1 to S4). Notably, one-half of the patients in both groups returned to a normal ABI at 1 month. This result was sustained at 12 months.

DISCUSSION

In the BIOLUX P-II trial, clinical and performance outcomes did not differ significantly between patients treated with DEB and patients treated with PTA. Therefore, the primary study hypothesis, a 45% relative risk reduction for binary restenosis, was not met. As in the IN.PACT-DEEP (Study of IN.PACT Amphirion™ Drug Eluting Balloon vs. Standard PTA for the Treatment of Below the Knee Critical Limb Ischemia) (12): 1) no biological efficacy of the drug coating could be observed; and 2) the safety and performance outcomes for the PTA group were surprisingly good. In contrast to IN.PACT-DEEP, there was no safety signal in the BIOLUX P-II trial, and the DEB group had numerically less major amputations of the target extremity (n = 1, 3.3% vs. n = 2, 5.6% for the overall study population, and 4.3% vs. 7.1% in CLI patients; p = NS); no additional major amputation occurred beyond 6 months. Yet, when interpreting the results, it has to be considered that the trial was not powered to detect differences in clinical outcomes.

Overall, the results obtained in BIOLUX P-II were good in both groups. For CLI patients treated in German hospitals, Malyar et al. (2) reported in-hospital mortality and major amputation rates of

8.4% and 3.5% for CLI patients. In BIOLUX P-II DEB patients with CLI at baseline, results were far better, with a 30-day mortality and major amputation rate of 0%. Furthermore, Conte et al. (13) suggested objective performance goals (OPGs) for treatment of patients with CLI and infrapopliteal lesions such as the following: 30-day safety OPGs for major amputation 4%, 1-year OPGs for limb salvage, and survival of 82% and 80%. In our series, both treatment arms were far below those values.

Compared with other trials with DEBs in infrapopliteal lesions, BIOLUX P-II had the smallest vessel diameter (2.3 mm vs. 2.5 to 2.9 mm [12,14,15]), which might have influenced revascularization rates. Late lumen loss was 0.56 mm for the DEB group and 0.54 mm for the PTA group in the BIOLUX P-II trial at 6 months compared with 0.61 and 0.62 mm at 12 months in IN.PACT-DEEP (12). Major amputation at 12 months was 3.3% for the overall DEB cohort and 4.3% in DEB-CLI patients compared with 0% (14), 4.4% (15), and 8.8% (12) reported in the published data. Despite the comparable angiographic parameters, 12-month TLR rate in the BIOLUX P-II trial was considerably higher than in other series (30.1% for DEB and 30.6% for PTA compared with 11.9% and 13.9% in IN.PACT-DEEP [12], 18% and 29% in DEBATE-BTK (Drug-eluting balloon in peripheral intervention for below the knee angioplasty evaluation) [14], and 17.3% in a single-center nonrandomized series [15]). This difference might be best explained by the fact that the BIOLUX P-II trial did mandate a 6-month angiography, whereas for IN.PACT-DEEP (12) and DEBATE-BTK (14), the angiographic assessment was performed at 12 months. It is very likely that investigators treated even clinically asymptomatic restenosis or occlusions during the 6-month angiography. That assumption is underlined by the fact that 80% of the TLR in the DEB group were done at the 6-month angiography, and the TLR curve increases sharply around 6 months.

The ability to compare the results of BIOLUX P-II to those of DES in infrapopliteal lesions is hampered, as most of the DES trials have been conducted in short lesions. Baumann et al. (16) have summarized the most relevant studies conducted with DES (Achilles, Destiny [Drug Eluting Stents In The Critically Ischemic Lower Leg], Below, Yukon BTK Trial, and a study by Falkowski et al.). In these studies, primary patency ranged from 84.0% to 91.0% at 6 months and from 77.6% to 85.0% at 12 months; however, the maximum average lesion length was only 31 mm. One small, single-center study in 50 patients compared a paclitaxel-eluting stent with a paclitaxel-eluting balloon in long infrapopliteal lesions (≥70-mm

TABLE 3 Procedural Characteristics

	DEB	PTA	p Value
Inflow lesions treated	18 (50.0)	11 (30.6)	0.093
Pre-dilation performed	42 (87.5)	15 (32.5)	<0.001
Pre-dilation balloon diameter, mm	1.9 ± 0.3	2.1 ± 0.4	0.027
Maximum pressure applied, atm	8.7 ± 2.0	8.4 ± 1.8	0.683
Cumulative inflation time pre-dilation, s	50.1 ± 28.3	33.4 ± 14.9	0.010
Device diameter, mm	2.5 ± 0.4	2.5 ± 0.5	0.851
Pressure applied at first inflation, atm	8.4 ± 3.3	7.9 ± 2.0	0.861
Inflation time first inflation, s	89.9 ± 44.8	71.7 ± 40.2	0.007
Device success (device based)	68 (91.9)	61 (93.8)	0.750
Technical success (lesion based)			
<30% residual stenosis	26 (54.2)	31 (59.6)	0.687
<50% residual stenosis	43 (89.6)	47 (90.4)	>0.999
Procedural success (patient based)	34 (94.4)	30 (83.3)	0.260

Values are n (%) or mean ± SD

Abbreviations as in Table 1.

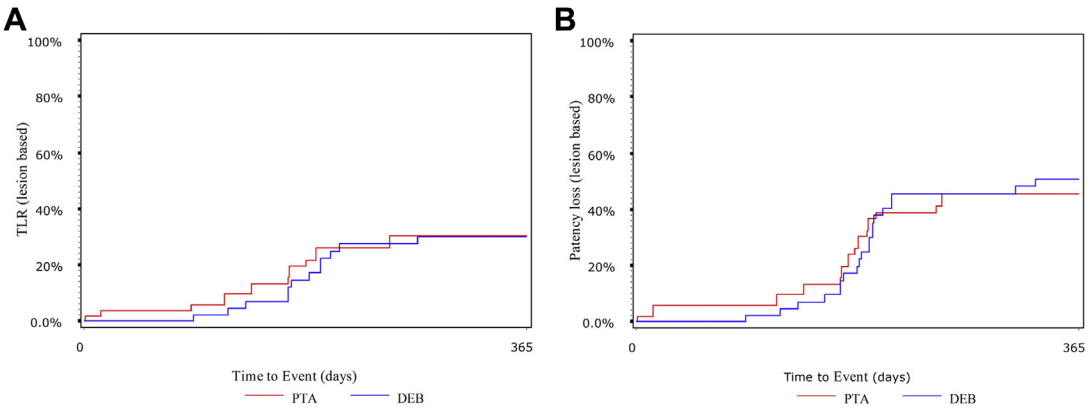
TABLE 4 Time-To-Event Estimates of Clinical Outcomes at Follow-Up

	DEB	PTA	p Value
180 Days			
MAE	8 (24.8)	9 (25.0)	0.944
Death	2 (6.1)	1 (2.9)	0.499
In CLI patients only	1 (4.0)	1 (3.7)	0.921
Amputation target extremity	8 (23.7)	7 (19.6)	0.619
Major	1 (3.3)	2 (5.6)	0.631
TLR lesion	6 (14.6)	10 (19.7)	0.460
Subject based	5 (16.8)	6 (17.5)	0.881
TVR	5 (16.8)	6 (17.5)	0.881
Target lesion thrombosis	0 (0.0)	1 (2.8)	>0.999
Patency loss (lesion based)*	7 (17.1)	13 (26.1)	0.298
365 Days			
MAE	13 (41.1)	14 (39.1)	0.957
Death	3 (9.4)	2 (6.0)	0.575
In CLI patients only	2 (8.6)	2 (7.9)	0.917
Amputation target extremity	8 (23.7)	9 (25.7)	0.988
Major	1 (3.3)	2 (5.6)	0.631
In CLI patients only	1 (4.3)	2 (7.1)	0.636
TLR			
Lesion based	12 (30.1)	15 (30.6)	0.805
Subject based	10 (34.9)	10 (30.0)	0.817
Clinically driven TLR, subject based	9 (31.3)	9 (26.9)	0.805
TVR	10 (34.9)	10 (30.0)	0.817
Target lesion thrombosis	0 (0.0)	1 (2.8)	>0.999
Patency loss (lesion based)*	20 (50.8)	22 (45.6)	0.908

Values are n (%). *Per core laboratory analysis.

CLI = critical limb ischemia; MAE = major adverse events (composite of all-cause death, major amputation of target extremity, target lesion thrombosis, and target vessel revascularization); TLR = target lesion revascularization; TV = target vessel; TVR = target vessel revascularization; other abbreviations as in Table 1.

FIGURE 2 Course of Target Lesion Revascularization and Patency Loss Per Kaplan-Meier Estimates



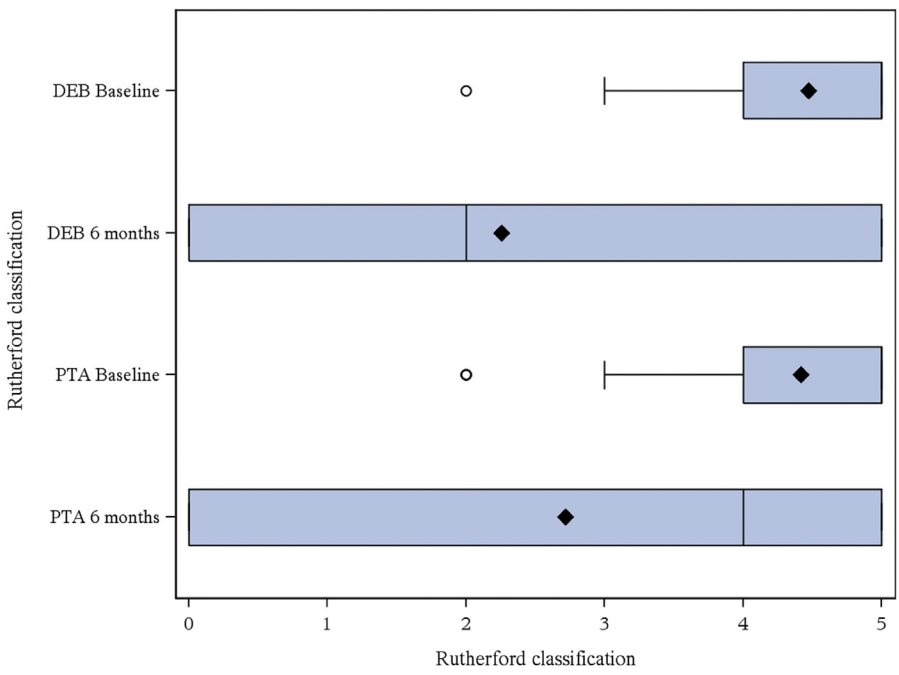
(A) Target lesion revascularization; **(B)** patency loss. Data are lesion based. Abbreviations as in Figure 1.

lesion length). With a mean lesion length of 127 mm in the DES group and 148 mm in the DEB group, 6-month binary restenosis was 28% in the DES group versus 58% in the DEB group ($p = 0.046$) and TLR was 7.7% versus 13.6% ($p = 0.65$), respectively (17).

What are potential reasons for the negative study outcome?

1. In the BIOLUX P-II trial, PTA lesions were significantly less calcified at baseline compared with DEB lesions—a known predictor for reduced DEB efficacy in PAD (18).
2. Difference in pre-dilation requirements and dilation time might have biased outcomes, as this might have caused additional trauma. Eventually,

FIGURE 3 Box Plots of Rutherford Classification at 6 Months Compared With Baseline



The **ends of the boxes** represent the first and third quartiles, the **vertical line** the median, the **solid diamond** the mean, and the **end of the whiskers** the minimum and maximum. **Open circles** = the lowest Rutherford category at baseline. Abbreviations as in Figure 1.

the techniques of angioplasty in infrapopliteal lesions need to be re-evaluated in respect to balloon sizing, inflation time, repetitive inflations, and inflation and deflation times.

3. Kashyap et al. (19) showed that angiography underestimates the degree of stenosis and calcification and overestimates the luminal diameter in tibial arteries compared with histological assessment. This may lead to a suboptimal sizing of interventional devices such as balloon angioplasty catheters. Adjunctive imaging assessment, such as intravascular ultrasound, may be useful for ensuring an optimized device sizing and hence improving durability of the intervention.
4. A potential explanation for different outcomes of DEB angioplasty in femoropopliteal lesions compared with infrapopliteal lesions might be drug-loss during advancement to the lesion with small diameter, as discussed for In.Pact Amphirion (Medtronic, Fridley, Minnesota) (20,21).

There are still a variety of unanswered questions. Studies are needed to better understand the drug delivery in infrapopliteal lesions, to better understand the effect of angioplasty in this vessel area, to assess to which extent additional imaging modalities might improve clinical outcomes, and to assess which treatment is best suited for a specific patient population.

STUDY LIMITATIONS. The BIOLUX P-II trial included only a small number of patients presenting with claudication and CLI. Furthermore, no wound healing was assessed. The mandated angiography at 6 months led to an artificial increase in TLR and made it difficult to distinguish between true clinically driven revascularizations and revascularizations that were done based on angiographic parameters. To avoid such bias, future studies should include a clinical follow-up at 12 months and the angiographic follow-up thereafter.

CONCLUSIONS

In a small patient population including claudicants and CLI patients, DEB treatment has proven to be safe, with comparable outcomes to PTA. Future studies are needed to better understand the underlying mechanisms in this complex lesion setting and to define patient groups that might benefit from DEB treatment.

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PERSPECTIVES

WHAT IS KNOWN? DEBs have proven to be superior to uncoated balloons in femoropopliteal lesions, but recent data for infrapopliteal lesions obtained from the IN.PACT-DEEP trial were discouraging.

WHAT IS NEW? We compared a novel DEB with a BTHC excipient (Passeo-18 Lux) to an uncoated balloon (Passeo-18) in a small series of patients with infrapopliteal lesions. Although the overall results were good and Passeo-18 Lux DEB proved to be safe, outcomes were not superior to uncoated balloons as seen in femoropopliteal lesions.

WHAT IS NEXT? Future studies are needed to better understand the mechanism of DEB treatment in infrapopliteal lesions and to identify patient and lesion groups that may benefit from this treatment option.

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KEY WORDS below-the-knee, critical limb ischemia, drug-coated balloon, drug-eluting balloon, infrapopliteal, peripheral artery disease

APPENDIX For supplemental tables, please see the online version of this article.